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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,254	04/04/2005	Esther M. Sternberg	4239-66912-02	5499

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,254	STERNBERG ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *4,10,11 and 16-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/5/06; 6/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I (claims 1-15) in the reply filed on 11/21/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that Applicant did not elect a species as for restriction requirement mailed on 8/22/2007. To follow this up, the Examiner contacted applicants' attorney Gillian L. Bunker on12/10/2007 to follow-up on this. Attorney Bunker made a telephonic election of species (i.e., nuclear receptor: GR; and bacterial product/toxin: LF) to facilitate the examination process.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, And/Or Claims

Claims 1-51 are pending.

Claims 4, 10-11 and 16-51 are withdrawn for being drawn to a non-elected invention.

Claims 1-3, 5-9 and 12-15 are being examined to the extent they read on the elected species (i.e., GR and LF)

Information Disclosure Statement

The information disclosure statements (IDSs) filed on 4/5/2006 and 6/14/2007 have been considered.

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/US03/31406, filed 10/3/2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a).

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Objections

claim 1 is objected because the claim recites a viable cell comprising "a nuclear hormone receptor substrate, or reporter construct, or both," wherein expression of the substrate reporter construct is detectable. It is not clear whether a nuclear hormone receptor is substrate and reporter construct are two separate entities (as it says "both") or it is a single entity as recited "the reporter substrate construct."

Claims 2 and 9 are objected for reciting a non elected invention (i.e., nuclear receptor such as AR, MR, TR, PR.....IRs, steroid receptor and thyroid receptor (claim 2); and a metalloenzyme of C. botulinum bacteria (claim 9).

The Examiner suggests that syntax of claim 1 can be improved by the following amendments:

Replace "nuclear hormone receptor pathway activity" to "a nuclear hormone receptor activity"

Replace "nuclear hormone receptor activity" to "said nuclear hormone receptor activity or the nuclear hormone receptor activity"

Replace "a viable cell" with "a test cell" or something like that.

It is not clear how a test cell is different from a control cell and if a test cell is a viable cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

For the purpose of comparing the claims with the prior art, it is noted that a nuclear hormone substrate is being interpreted as any gene or substrate to which said NR binds and modulates the substrate.

Claims 1, 2, 5-6, 7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Aranda and Samuels (J. Biol. Chem. 259:6110-6116, 1984).

Claims 1, 2, 5-6, 7, 12 and 13 are broadly drawn to a method of identifying an agent that modulates the activity of a nuclear hormone receptor(NR) comprising (i) providing a viable cell that expresses a NR and a NR substrate, receptor construct, or both; wherein expression of the substrate reporter construct is detectable and provides a measurement of NR pathway activity; (ii) contacting a test cell with a test agent and an isolated bacterial product; (iii) contacting a control cell with the isolated bacterial product in the absence of the agent; (iv) detecting and comparing nuclear hormone receptor activity between the test and control cell to identify a test agent that interacts with the NR and modulates the activity of the NR by the bacterial product, wherein the nuclear hormone is selected from a GR, PR, AR, MR, thyroid hormone receptor,....and thyroid receptor (claim 2), wherein the bacterial product is a bacterial wall protein, soluble bacterial protein or lipoplysaccharide (claim 5), wherein the bacterial product is a bacterial toxin that is not endotoxin (claim 6), and wherein toxin elicits one or more symptoms of a toxic effect (claim 7), wherein the agent exerts its effects on the NR through a mechanism other than a MEK1 or MAPPKK pathway (claim 12), wherein the agent is a genetically engineered or chemically modified variants or mimetic of the bacterial product or a drug or a cofactor of the NR (claim 13), and wherein the agent is effective following administration to a mammal subject to reduce one or more inflammatory and/or autoimmune symptoms that can accompany exposure to the bacterial product or infection by a pathogen expressing the product (claim 13).

Aranda and Samuels teach that thyroid hormone action is mediated through nuclear thyroid hormone receptor (TR) which is an acidic DNA binding protein (page 6110, left column). They teach that a number of nutritional, pharmacological, or physiological factors may interact to modulate the levels of receptor and may potentially influence the cell response to thyroid hormone (page 6110, right column). They teach that cholera toxin elicits a dose-dependent response in depleting the thyroid hormone NR (page 6110, right column second paragraph). They teach measuring the thyroid hormone NR using labeled T3 (see Quantitation of Thyroid Hormone Nuclear Receptor Levels, page 6111). Aranda and Samuels teach measuring binding of labeled Thyroxin to the thyroid hormone NR in the presence or absence of cholera toxin (see Figure 1, page 6111 and Figure 11, page 6115).It is well known in the art that cholera toxin is a soluble protein enzyme (ADP-ribosyltransferase) (see Schmitt et al Emerging Inf. Dis. 5: 224-334, 1999). It is noted that Schmitt et al is applied to support the state of the art and not as a prior art. Aranda and Samuels teach that cholera toxin decreases the level of thyroid hormone receptor (Results, page 6111). They teach that cholera toxin does not alter cell growth rate as reflected from data on the total DNA and protein estimation (page 6111, right column). This suggests that the cholera toxin is not endotoxic. It is well known in the art that cholera toxin produces a toxic effect (Schmitt et al). It is noted that Schmitt et al is applied to support the state of art and not as a prior art. Aranda and Samuels teach that L-T3 elicits a reduction in receptor solely by decreasing the accumulation of newly synthesized receptor (in vitro using GH1 cells) and the decrease in receptor does not happen in vivo in rat liver (page 6110, right column). Aranda and

Samuels do not explicitly teach a role of thyroxine (or triidothtyronine) in inhibiting inflammation. It is well known the art that the drug thyroxine when administered in a mammal inhibits inflammatory response (inherent property). Rittenhouse and Redei (Endocrinology, 138: 1434-1439, 1997) teach that thyroxine inhibits inflammation produced by streptococcal cell wall when administered to a mammal. It is noted that the reference Rittenhouse and Redei to support the skill of the art and not as a prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aranda and Samuels in view of Sapnjaard et al (Endocrinology, 136: 5084-5092, 1995).

Claim 3 is further drawn to a method of identifying an agent that modulates the activity of a nuclear hormone receptor (NR) wherein the nuclear hormone receptor is GR.

The teachings of Aranda and Samuels are summarized as set forth supra. Aranda and Samuels do not teach the effect of a toxin on glucocorticoid receptor.

Sapnjaard et al teach that nuclear receptor TR is a transcription factor of a superfaimily to which steroid hormone receptors such as glucocorticoid (GR), retinoic acid, and vitamin D3 receptors belong (page 5084, 1st paragraph).

Therefore, it would have been prima facie obvious to one of the skill in the art to use GR from the steroid-retinoid-thyroid receptor superfamily to identify an agent that modulates the activity of glucocorticoid hormone receptor(GR) as taught by Sapnjaard et al. One of the skill in the art would have been motivated to use the GR of Sapnjaard et al as they teach that TR and GR are the members of the same NR superfamily. One of the skill would have a reasonable success in replacing a screening assay of TR with GR because Sapnjaard et al teach that NR and GR belong to the same superfamily of nuclear receptors and because modifying a screening assay from one nuclear receptor to another nuclear receptor is routine in the art.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aranda and Samuels in view of Schmitt et al. (Emerging Inf. Dis. 5: 224-234, 1999).

Claims 8 and 9 are further drawn to a method of a method of identifying an agent that modulates the activity of a nuclear hormone receptor (NR) by contacting a test agent and an isolated bacterial toxin, wherein the bacterial toxin exhibits

metalloprotease activity and wherein the bacterial toxin is anthrax lethal factor (LF) or lethal toxin (LeTx).

The teachings of Aranda and Samuels are summarized as set forth supra. Aranda and Samuels et al do not teach using a metalloprotease bacterial toxin wherein the bacterial toxin is LF or LeTx.

Schmitt et al teach that a number of bacterial toxins have been identified as the primary virulence factor(s) for a variety of pathogenic bacteria. They teach a number of bacterial toxins and their mode of action in the Table: Characteristics of bacterial toxins (page 225). They teach that anthrax lethal factor is a metalloprotease (see page 225).

Therefore, it would have been prima facie obvious to one of the skill in the art to use any bacterial toxin including metalloprotease anthrax lethal factor to replace cholera toxin in identifying an agent that modulates a NR activity as taught by Schmitt et al. One of the skill in the art would have been motivated to use bacterial a number of toxins including metalloprotease anthrax LF to identify an agent that modifies a nuclear receptor because Schmitt et al teach various bacterial toxins and their virulence factor(s). One of the skill would have a reasonable success in using bacterial metalloprotease anthrax LF because Schmitt et al teach that anthrax LF is a toxin.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Robert Landsman/
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